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(54) Title: RAPID SETTING HYDROXYLAPATITE AND PLASTER FORMULATION

(57) Abstract

Compositions for use in bone implantation, repair and reconstruction comprising calcium sulfate hemihydrate, hydroxylapatite and sodium sulfate. The sodium sulfate enables the composition to be used in the presence of blood or other body fluids.

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RAPID SETTING HYDROXYLAPATITE AND PLASTER FORMULATION

Background of the Invention

1. Field of the Invention

This invention relates to formulations useful in bone and dental implant, repair and reconstruction. The formulations include mixtures of calcium sulfate hemihydrate, hydroxylapatite and sodium sulfate. The sodium sulfate has been found to greatly accelerate the hardening of the mixture in the presence of blood.

2. Description of the Related Art

U. S. Patent 4,619,655 discloses animal implants comprising a binder lattice or scaffold of calcium hemihydrate (plaster of paris) and a non-bioresorbable calcium material such as hydroxylapatite. In U.S. Patent 4,681,644 calcium sulfate hemihydrate is described as hardening in water in about thirty (30) minutes.

Calcium sulfate hemihydrate (plaster of Paris) has been known for years to have excellent reparative qualities in bone defects, but ordinarily it is quickly resorbed. A composite of a dense form of plaster of Paris and hydroxylapatite provides nonresorbable hydroxylapatite particles for bone to form around and within during the phase of plaster absorption.

It is known that calcium sulfate hemihydrate compositions set poorly in the presence of blood and other proteinaceous body fluids. Outside of the body, many chemical additives may be used to deliberately

accelerate or retard setting. In the body, however, body fluids contribute chemicals which upset the delicate balance between retardation and acceleration of plaster setting.

As the dihydrate forms, the concentration of chemicals such as sodium chloride increases. This causes the remaining water to be supersaturated. Salt crystal formation on the nuclei of crystallization of the gypsum "poisons" the nuclei. This retards further crystallization, upsetting the delicate balance.

Thus, although some compounds are listed as known accelerators, in the body they may act as set retardants. One of the inventors of U.S. Patent 4,619,655 has published a paper which states that set retardation in blood may be controlled by the addition of 10% potassium sulfate or 16.7% sodium chloride. These high concentrations may cause salt crystal formation due to the increased potassium ion levels. Additionally, the concentrations employed may be harmful to the body. The sterilized gypsum-accelerated product is not fully acceptable because the shelf-live is only eight months due to pre-implantation characteristics. Also, since gypsum is not water soluble, the gypsum must be mixed into the dry powders. Since very little gypsum is needed, it is difficult to assure a uniform and homogeneous mixture with gypsum.

The art described in this section is not intended to constitute an admission that any patent, publication or other information referred to herein is "prior art" with respect to this invention, unless

specifically designated as such. In addition, this section should not be construed to mean that a search has been made or that no other pertinent information as defined in 37 C.F.R. § 1.56(a) exists.

Summary of the Invention

The invention provides a composition useful in dental, orthopedic and neurological procedures involving bone implant, repair or reconstruction. The composition includes calcium sulfate hemihydrate (plaster of paris), hydroxylapatite and sodium sulfate to accelerate and control the setting. "Hydroxylapatite" as used herein may include variations of resorbable and non-resorbable calcium phosphates, including the resorbable trichloryl phosphate form. The sodium sulfate provides superior acceleration in the presence of blood. It is employed in the range of 1.5 to 4 % by dry weight based on the weight of calcium sulfate hemihydrate.

Screening studies were undertaken to seek an accelerant that would be stable in the presence of blood. Potassium oxalate and sodium heparin blood tubes were found to be useful. It was found that sodium citrate and EDTA acted as a setting retardant. Calcium hydroxide and deionized water did not function as an accelerant in the presence of blood. Ferrous sulfate provided acceleration but has an inadequate shelflife.

Potassium sulfate at 0.85% by weight of the calcium sulfate hemihydrate provided acceleration.

However, questions concerning its toxicity eliminated its use as an accelerator in vivo. Also, at these levels the potlife is not optimum. "Potlife" refers to the working time of the mixture. When the plaster begins to set the mixture becomes cohesive and putty-like. At the end of its useful potlife, the material becomes gritty and does not hold together well. The potlife expires when the material loses its smooth, soft nature or when the material becomes gritty and does not stick together.

The individual chemicals present in a potassium oxalate blood tube were suspected of being accelerants. Testing of the chemicals found that sodium sulfate is an accelerant in the presence of blood. Although sodium sulfate is not an additive to the blood tubes, both the sodium and sulfate ion are present. The inventors recognized that the contributions of the ions in the blood tube could be reproduced by employing sodium sulfate in the plaster formulation. Sodium sulfate had not been tested previously since it was known to be an inferior accelerator for plaster of paris as compared to potassium sulfate, gypsum and potassium chloride based on literature reviews and laboratory bench work.

Description of the Preferred Embodiments

Hydroxylapatite (HA) has been commonly used in dental applications of periodontal defect filling and ridge augmentation since the 1970's. HA is a biocompatible substance functioning as a non-resorbable scaffold for new bone growth.

HA alone is not readily used in orthopedic applications because it does not maintain a cohesive mass during delivery and placement in the implant site. Calcium sulfate hemihydrate (plaster of paris) is used in conjunction with HA to produce a more deliverable and implantable composition which minimizes migration of particles from the site to an undesired location.

Calcium sulfate hemihydrate hardens into a dihydrate form known as gypsum. Gypsum is completely resorbed from the site in the body in about four to six weeks. HA is preferably used in about a 65% to 35% calcium sulfate hemihydrate mixture to provide enough plaster to fill the gaps between the HA particles. Higher plaster levels results in loss of implant volume during plaster resorption. Lower plaster levels result in a less cohesive mass of particles for delivery. Again, resorbable or non-resorbable forms of calcium phosphates may be employed in this invention.

"Set" is the crystallization of calcium sulfate dihydrate (gypsum) from calcium sulfate hemihydrate in the presence of water. "Hardening" is a measure of compressive strength development in calcium sulfate hemihydrate as set occurs. It is dependent on the chemical crystallization "set" process. Hardening may be gauged by a Vicat set test, ASTM C-472.

EASE OF USE

Following combination of the dry ingredients and water, the components must be thoroughly mixable within about thirty seconds, and transferrable to the defect site within one minute.

POT LIFE

The formulation should provide a working time of between two and five minutes. This is defined as the length of time that the product remains moldable and thus implantable in a defect site.

MOLDABILITY

The product must be able to be molded down and packed into an implant site, such that the void is completely filled. The material should not fall out of the site due to the effects of gravity.

SETTING TIME IN SITE

In order to achieve the control of particle migration, the product must lose its moldability in the site within about ten minutes of placement. In addition, it must harden within about one hour of placement.

EXAMPLE

Hydroxylapatite/calcium sulfate hemihydrate compositions were prepared in a 65:35 ratio by weight and were wetted with 0.9% saline solution. The material immediately softened upon implantation and did not harden within the desired time limit. It appeared as though the plaster portion was dissolving in contact with the blood. "Tamping" of the mixture into the site only resulted in further flowage of HA particles from the site. Likewise, the material could not be wiped up with a swab, which instead drew the plaster-portion up further. The nearly set (hardened) mixture softened immediately even in contact with minimal blood.

EXAMPLE II

Hydroxylapatite/calcium sulfate hemihydrate compositions were prepared in a 65:35 ratio by weight and were wetted with 0.9% saline solution. Sodium sulfate was added by weight percent by weight of calcium sulfate hemihydrate.

Sodium sulfate accelerated compositions provided better set times in blood than the use of potassium sulfate. It could be uniformly supplied to the original powder unlike the addition of gypsum as an accelerant. The following table compares sodium sulfate to potassium sulfate as an accelerant.

Minutes	Potassium Sulfate	Sodium Sulfate
Potlife	< 2	2 < x < 4
Set Time (in blood)	> 45	4 < x < 45

The following table shows the set time and potlife of compositions using varying levels of sodium sulfate. As shown, sodium sulfate levels of less than about 1.5% or greater than about 4.0% have potlives which are not desirable.

% Sodium Sulfate (Dry)	Potlife (minutes)	Blood Set Time (minutes)
0	9.25	> 45
1.5	1.75	30*
2.4	2.25	30
3.4	3.0	30 < x < 45
4.0	5.0	30*

* Set with the exception of areas where blood had pooled

Further studies with the 2.4% and 3.4% formulas showed that blood set times are dependent on the consistency of the material when it is added to the blood, the harder the better. The extent to which the material was mixed with the blood also affected the end result. It has been found that the inclusion of sodium sulfate in the range of 1.5 to about 4.0 % by weight based on weight of calcium sulfate hemihydrate will provide a superior product. The compositions of the invention maintain their cohesiveness in blood better than previous formulations.

Presently, the preferred level of sodium sulfate is between about 2.35 and about 2.45% by weight per calcium sulfate hemihydrate by weight for dry sodium sulfate. However, when sodium sulfate is added as a solution, the preferred range increases to as much as 3.5%.

While this invention may be embodied in many different forms, there are shown in the drawings and

described in detail herein specific preferred embodiments of the invention. The present disclosure is an exemplification of the principles of the invention and is not intended to limit the invention to the particular embodiments illustrated.

This completes the description of the preferred and alternate embodiments of the invention. Those skilled in the art may recognize other equivalents to the specific embodiment described herein which equivalents are intended to be encompassed by the claims attached hereto.

WHAT IS CLAIMED IS:

1. A composition for use as an animal implant comprising calcium sulfate hemihydrate, calcium phosphate and between about 1.5 to about 4.0 percent sodium sulfate by weight based on calcium sulfate hemihydrate.

2. The composition of Claim 1 wherein said sodium sulfate comprises between about 2.35 to about 3.5 percent by weight of the composition.

3. The composition of Claim 1 further including a wetting agent selected from the group consisting of water, saline, blood and mixtures thereof.

4. The composition of Claim 1 wherein said calcium phosphate is hydroxylapatite, and the hydroxylapatite and calcium sulfate hemihydrate are in a ratio of about 65 to 35 percent by weight.

5. A composition for use as an animal implant consisting essentially of calcium sulfate hemihydrate and hydroxylapatite at a weight to weight ratio of about 35 to 65, and between about 1.5 to about 4.0 percent sodium sulfate by weight based on calcium sulfate hemihydrate.

6. The composition of Claim 5 wherein said sodium sulfate comprises between about 2.35 to about 2.45 percent by weight of the composition.

7. The composition of Claim 6 further including a wetting agent selected from the group consisting of water, saline, blood and mixtures thereof

8. A method for hardening calcium sulfate hemihydrate compositions in the presence of blood which comprises adding from about 1.5 to about 4.0 percent by weight sodium sulfate to the composition, contacting the composition with a wetting solution, initiating the

hardening reaction and thereafter placing the wetted composition in contact with blood or other proteinaceous material from an animal.

9. A composition for use as an animal implant having a set time of less than about 30 minutes and a pot life of between about two to five minutes comprising calcium sulfate hemihydrate, calcium phosphate and between about 1.5 to about 4.0 percent sodium sulfate by weight based on calcium sulfate hemihydrate.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/03208

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

U.S.CL.: 424/426, 529; 623/16; 106/645,650,772,774,775,776

IPC(5): A61F 2/28; A61K 9/00, 35/14; C04B 11/06

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	424/426,529; 623/16; 106/645,650,772,774,775,776

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

CAS, BIOSIS, APS

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	US.A. 2.862.829(Dixon. Jr. et al) 02 December 1958. see the entire document	1-9
Y	US.A. 3.303.030 (PRESTON) 07 February 1967. see the entire document.	1-9
Y	Proceedings of the 44th Annual Meeting of the Electron Microscopy Society of America. issued 1986. Hanker et al.. "Setting of Composite Hydroxylapatite/ Plaster Implants with Blood for Bone Reconstruction." pages 328-329. see the entire document.	1-9

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
20 June 1991	20 SEP 1991
International Searching Authority	Signature of Authorized Officer
ISA/US	Jean C. Witz

Form PCT/ISA/210 (second sheet) (Rev.11-87)